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Canadian Adverse Reaction Newsletter

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Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Contact Health Canada or a Regional AR Centre free of charge

Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Form available at:

www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf

Bisphosphonates and ocular disorders

Bisphosphonates inhibit bone resorption. Indications for their use vary according to the individual products, but they are used primarily to prevent or treat osteoporosis, Paget's disease of bone, tumour-induced hypercalcemia and conditions associated with increased osteoclast activity (predominantly lytic bone metastases and multiple myeloma). International data from spontaneous reporting systems for visual reactions associated with bisphosphonates suggest that, in rare instances, this class of medication can cause serious ocular adverse effects.[1]

Pamidronate has been associated with ocular inflammation such as uveitis, nonspecific conjunctivitis, episcleritis and scleritis.[1] Similar disorders have been linked to alendronate, clodronate, etidronate and risedronate.[1–3] These ocular effects were initially thought to be related to amine-bisphosphonates, which include alendronate, pamidronate and risedronate. However, clodronate and etidronate, both non-amine-bisphosphonates, have also been implicated.[1–3]

Health Canada received 27 domestic reports of suspected ocular and visual disorders associated with bisphosphonates since their introduction to the Canadian market to Feb. 28, 2003 (Table 1). Of these reports, 13 involved alendronate, 5 etidronate, 6 pamidronate and 3 risedronate. No cases of visual disorders have yet been reported in association with clodronate or zoledronic acid in Canada. Many factors, such as time marketed, exposure data and varying indications for the different products, can influence reporting rates of adverse effects in spontaneous reporting systems.

Indications of ocular inflammation may include eye pain, redness, abnormal vision (blurred or double vision, decreased vision, "floaters") and

Table 1: Reactions described in the 27 reports submitted to Health Canada of suspected domestic adverse reactions (ARs) of visual disorders associated with bisphosphonates from date marketed in Canada to Feb. 28, 2003*

Variable	Alendronate	Etidronate	Pamidronate	Risedronate
Date marketed in Canada	1996	1979	1992	1999
Reaction terms reported† (no. of reactions)	Abnormal vision (5),‡ blindness (1),§ conjunctivitis (2), corneal ulceration (1), eye pain (4), iritis (2), lacrimation abnormal (1), periorbital edema (2)	Abnormal vision (2),‡ blindness (1),§ blindness temporary (1), conjunctivitis (1), keratitis (1), macula lutea degeneration (1), photopsia (1), retinal disorder (1)	Abnormal vision (4),‡ eye pain (1), optic neuritis (1), periorbital edema (1), photophobia (1), pupillary reflex impaired (1)	Blindness (2),§ glaucoma (1), ocular hemorrhage (1), retinal detachment (1)

***These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.** These reactions are not limited to ocular inflammation but include all reported visual disorder reactions. Spontaneous reports are considered suspicions only.
†Several reaction terms may be listed per AR report. Reaction terms are based on the "preferred term" of the World Health Organization (WHO) *Adverse Reaction Dictionary* (WHOART).
‡Includes blurred vision and decreased vision.
§Describes various degrees of decreased vision.

photophobia.[1,4] Although these ocular effects may be rare with bisphosphonates, health care professionals should be aware of their possibility. The following guidelines have been suggested for the care of patients receiving bisphosphonates:[1]

- Patients with visual loss or ocular pain should be referred to an ophthalmologist.
- Nonspecific conjunctivitis seldom requires treatment and usually decreases in intensity during subsequent exposure to a bisphosphonate.
- More than 1 ocular side effect can occur at the same time (e.g., episcleritis in conjunction with uveitis). In some instances, the drug may need to be discontinued in order for the ocular inflammation to resolve.
- For scleritis to resolve, even during full medical therapy, the bisphosphonate therapy must be discontinued.

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Fluticasone and adrenal suppression

Inhaled corticosteroids are highly effective for the control of asthma and the prevention of exacerbations.[1] Recently, there have been several reports worldwide of adrenal insufficiency in adults and children using inhaled corticosteroids.[2-5] Although adrenal insufficiency can occur with any inhaled corticosteroid, it may be more common with fluticasone because of the drug's pharmacologic and pharmacokinetic properties, including its greater potency and hence lower equivalent dose (half the dose of either budesonide or beclomethasone).[2,6,7] In addition, this may result from higher-than-licensed doses of fluticasone being more widely prescribed in children than other inhaled corticosteroids.[5]

The Health Canada database was searched for suspected adverse reactions involving endocrine disorders reported from Jan. 1, 1996, to Sept. 30, 2002, associated with fluticasone, budesonide and beclomethasone. There were no Canadian case reports of suspected adrenal insufficiency associated with the use of budesonide or beclomethasone.

There were 9 reports involving fluticasone, 5 of which involved children aged 4–13 years (where specified). Dosages (where specified) ranged from 250 to 1100 µg/d; in 4 cases the dose exceeded 1000 µg/d. Two patients experienced adrenal crisis; one was a boy (age unspecified), and the other was a 72-year-old man.

Adrenal insufficiency associated with inhaled corticosteroid use can occur because of systemic absorption of the corticosteroid and consequent suppression of endogenous glucocorticoids, which leaves insufficient adrenal reserve to respond to stressful stimuli (e.g., surgery, trauma and infection).[2,3] Adrenal insufficiency may also result from abrupt discontinuation or noncompliance with treatment, which leads to acute steroid deficiency.[2,3] Signs and symptoms of adrenal suppression and crisis are nonspecific and include anorexia, abdominal pain, weight loss, fatigue, headache, nausea, vomiting, decreased level of consciousness, hypoglycemia and seizures.[3,5]

Clinicians are reminded that, beyond a certain limit, increasing the dose of inhaled corticosteroids offers minimal benefit but increases the risk of systemic adverse effects.[1,7,8] Canadian asthma consensus guidelines recommend that, once best results are achieved, the dose should be reduced at appropriate intervals to determine the minimum dose required to maintain control.[1] In addition, different inhalation techniques (e.g., chambers, inhalers and spacers) and propellants (e.g., chlorofluorocarbon v. hydrofluoroalkane preparations) can influence the portion of inhaled drug, and thus systemic bioavailability.[8,9]

Patients and parents should be informed of the risk as well as the signs and symptoms of adrenal suppression associated with the use of inhaled corticosteroids. Adrenal suppression can be reversed upon reduction of dosage. However, patients and parents should also be cautioned about the risk of serious adverse reactions from abruptly stopping treatment.

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Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Adhesion prevention solutions in gynecological procedures: late-onset postoperative pain

Intergel™ Adhesion Prevention Solution (0.5% ferric hyaluronate gel) is indicated in Canada for use as an intraperitoneal instillate for the reduction of adhesions following peritoneal cavity surgery.[1] It provides a transient, viscous, lubricious coating on peritoneal surfaces following surgical procedures. The product is contraindicated in patients with pelvic or abdominal infection. Health Canada issued a class III medical device licence (a class III medical device has relatively higher risk characteristics than class I and II devices; in this case, the product is surgically invasive) for the product on Sept. 21, 1999. Since then, there have been post-market reports of suspected late-onset postoperative pain and repeat surgeries following onset of pain, noninfectious foreign-body reactions and tissue adherence associated with certain gynecological procedures. In some patients residual material was observed during surgery.

On Mar. 28, 2003, Gynecare Worldwide, a division of Ethicon, Inc., the product distributor, issued an urgent worldwide voluntary withdrawal of Gynecare Intergel™ Adhesion Prevention Solution and advised that all use of the product be immediately discontinued.[2] The Canadian distributor issued an equivalent urgent recall on Apr. 2, 2003.[3] The Canadian recall was completed by May 6, 2003.

One report of a serious, unexpected reaction suspected to be associated with the product was received by Health Canada. A woman in her mid-30s (weight 64 kg) underwent laparoscopy and left fimbrioplasty in November 2002. Intergel™ Adhesion Prevention Solution was instilled at the end of the procedures. The following day the patient was admitted to hospital with peritonitis-like symptoms. She was given antibiotics empirically, and over 3 days her condition started to improve but she was still in pain. In January 2003 she presented with pelvic pain and was admitted to hospital for surgery. Residue of Intergel™ Adhesion Prevention Solution was washed out. Inflammation was observed, and many internal organs were adhered, with degradation of tissue.

The manufacturer of Gynecare Intergel™ Adhesion Prevention Solution is currently assessing technical issues, surgical techniques and circumstances associated with these post-market events and will communicate the results of its findings to Health Canada.

Health Canada, as well as other regulatory agencies, is closely monitoring the issue of acute aseptic reactions and acute foreign-body reactions associated with the use of bioresorbable anti-adhesion barrier products, such as Seprafilm™, Interceed™ and Sepracoat™. Health care professionals are encouraged to report any suspected or confirmed similar cases of late-onset postoperative pain and repeat surgeries that may have been associated with the use of Gynecare Intergel™ Adhesion Prevention Solution, or cases of postoperative acute aseptic peritonitis

Case Presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Intravenous immunoglobulin: suspected association with an intrauterine death

A 25-year-old woman was found to have idiopathic thrombocytopenic purpura (ITP) during pregnancy. She had no previous history of ITP and was otherwise healthy. Her platelet count was about 50 000 × 10^6/L during pregnancy, and ultrasounds of the fetus at 12 and 20 weeks' gestation appeared normal.

Intravenous immunoglobulin therapy was prescribed at 38 weeks' gestation in anticipation of an epidural anesthesia, given a recent drop in the platelet count to 43 000 × 10^6/L. The patient received the first infusion of immunoglobulin between 11:05 and 17:20. A few hours later, she noticed the absence of fetal movements. A second infusion was started at 9:10 the following morning but was stopped 25 minutes later when she mentioned the absence of fetal movements. An ultrasound confirmed intrauterine death.

Autopsy revealed signs of intrauterine growth retardation and hypoxia but no malformations. Mild maceration suggested that death might have occurred 24 to 48 hours earlier. However, examination of the placenta revealed multiple infarcts involving about 50% to 60% of its surface, and although one small infarct was believed to be old, the others showed histological changes consistent with infarcts 12 to 24 hours old.

The underlying condition that resulted in intrauterine growth retardation may also have played a role in this case. Postpartum hematological evaluation was negative for antiphospholipid antibodies. Although there is clinical evidence of a possible association between intravenous immunoglobulin therapy and thrombotic events, we are unaware of any other cases of massive placental thrombosis following the administration of this product.

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possibly associated with the use of other anti-adhesion products.

Any problems or complaints pertaining to medical devices should be reported to Health Canada at the address below, or through the toll-free number 800 267-9675.

Health Products and Food
Branch Inspectorate
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David F. Clapin, BSc, PhD, MPA; Philip Neufeld, PhD; Kim Dix, PEng, BASc; Fred Lapner, MD, FRCPC, Health Canada

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3. *Urgent voluntary recall of Gynecare Intergel™ Adhesion Prevention Solution.* Gynecare Worldwide; issued in Canada by Johnson & Johnson Medical Products, Markham, Ont.; 2003 Apr 2.

Summary of health professional and consumer advisories posted from May 31 to Aug. 31, 2003

Advisories are available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_e.html

Date	Product	Subject and type
Aug 19 & 18	Casodex®	Accelerated deaths using Casodex® (bicalutamide) 150 mg in patients with localized prostate cancer otherwise undergoing watchful waiting. Health Canada has withdrawn its approval (Notice of Compliance with conditions) for Casodex® 150 mg — AstraZeneca Canada Inc. — consumer information and health professional advisory
July 23	CYPHER™ Coronary Stent	Important medical devices safety information regarding CYPHER™ Coronary Stent and subacute thrombosis — Cordis Corporation — health professional advisory
July 18 & 17	GlucoNorm® (repaglinide) and gemfibrozil	Important safety information on the concomitant use of GlucoNorm® (repaglinide) and gemfibrozil — Novo Nordisk Canada Inc. — consumer information and health professional advisory
July 16 & May 28	Premplus™	Important safety information on estrogen plus progestin (Premplus™ tablets) — Wyeth Pharmaceuticals — consumer information and health professional advisory
July 17 & 11	TOPAMAX™	Important drug warning — reports of oligohidrosis (decreased sweating) and hyperthermia in patients treated with TOPAMAX™ (topiramate) — Janssen Ortho, Inc. — consumer information and health professional advisory
July 15 &10	Paxil®	Important drug warning — Paxil® (paroxetine hydrochloride) should not be used in children and adolescents under 18 years of age — GlaxoSmithKline — consumer information and health professional advisory
July 7	Counterfeit Lipitor®	Health Canada advises public of counterfeit Lipitor® in US — consumer information
June 25	Pan Pharmaceuticals Ltd.	Health Canada alerts Canadians to Pan Pharmaceuticals Ltd. recall in Australia — consumer information
June 16	Repaglinide and gemfibrozil	EMEA contraindicates the concomitant use of repaglinide and gemfibrozil — health professional advisory
June 9	*Ephedra*/ ephedrine	Health Canada reminds Canadians of the dangers of *Ephedra*/ephedrine products — consumer information
June 6	Empowerplus	Health Canada is advising Canadians not to use Empowerplus — consumer information
June 5	Insulin products	It's Your Health: insulin products in Canada — consumer information
May 9	Rapamune® (sirolimus)	Important drug safety information for lung transplant patients being treated with Rapamune® (sirolimus) — Wyeth Pharmaceuticals — consumer information

To receive the Newsletter and health product Advisories by email, join Health Canada's ***Health Prod Info*** mailing list. ***Go to*** **www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe_e.html**

"It's Your Health": insulin products

In June 2003, Health Canada updated an "It's Your Health" document on insulin products available in Canada, in consultation with diabetes patient groups. The document is available on Health Canada's Web site (www.hc-sc.gc.ca/english/iyh/medical/insulins.html). It has been updated to reflect concerns regarding the need for additional information about animal insulins and their existing availability. The updated version also includes information from a Cochrane systematic review that assessed the efficacy and safety profile of human and animal insulins.[1]

Reference

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Canadian Adverse Reaction Newsletter

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Suggestions?
Your comments are important to us. Let us know what you think by reaching us at cadrmp@hc-sc.gc.ca

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